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<p>(21) International Application Number: PCT/GB96/00587 (22) International Filing Date: 13 March 1996 (13.03.96) (30) Priority Data: 9505491.2 18 March 1995 (18.03.95) GB (71) Applicant (for all designated States except US): MERCK SHARP &amp; DOHME LIMITED [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HAWORTH, Karen, Elizabeth [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). OWEN, Simon, Neil [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). SEWARD, Eileen, Mary [IE/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). (74) Agent: HISCOCK, Ian, James; Merck &amp; Co., Inc., European Patent Dept., Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: MORPHOLINE DERIVATIVES, COMPOSITIONS CONTAINING THEM AND THEIR USE AS THERAPEUTIC AGENTS</p>		
<p>(57) Abstract</p>		
<p>The present invention relates to compounds of formula (I), wherein R<sup>1</sup> and R<sup>4</sup> represent hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkyl(C<sub>1-6</sub>alkyl), C<sub>1-6</sub>alkoxy, C<sub>1-6</sub>alkyl substituted by a hydroxy or C<sub>1-6</sub>alkoxy group, OCF<sub>3</sub>, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR<sup>a</sup>, SOR<sup>a</sup>, SO<sub>2</sub>R<sup>a</sup>, COR<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup> or CONR<sup>a</sup>R<sup>b</sup>, where R<sup>a</sup> and R<sup>b</sup> are each independently hydrogen or C<sub>1-6</sub>alkyl; R<sup>2</sup>, R<sup>3</sup> and R<sup>5</sup> represent hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy substituted by a C<sub>1-6</sub>alkoxy group, or trifluoromethyl; R<sup>6</sup> represents C<sub>1-6</sub>alkyl, optionally substituted by oxo, substituted by a 5-membered heteroaromatic ring selected from oxazole, thiazole, isoxazole, isothiazole, oxadiazole and thiadiazole, wherein each heteroaromatic ring is substituted at the available carbon atom by a group of the formula: ZNR<sup>7</sup>R<sup>8</sup>. The compounds are of particular use in the treatment of pain, inflammation, migraine and emesis.</p>		
<div style="text-align: center;"> <p>(I)</p> </div>		

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**MORPHOLINE DERIVATIVES, COMPOSITIONS CONTAINING  
THEM AND THEIR USE AS THERAPEUTIC AGENTS**

This invention relates to a class of morpholine compounds which are  
5 useful as tachykinin antagonists. More particularly, the compounds of the  
invention are N-substituted morpholine derivatives bearing a  
heteroaromatic moiety.

The tachykinins are a group of naturally occurring peptides found  
widely distributed throughout mammalian tissues, both within the central  
10 nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal  
sequence:

Phe-X-Gly-Leu-Met-NH<sub>2</sub>

At present, there are three known mammalian tachykinins referred  
15 to as substance P, neurokinin A (NKA, substance K, neuromedin L) and  
neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides*  
(1985) 6(suppl. 3), 237-242). The current nomenclature designates the  
three tachykinin receptors mediating the biological actions of substance P,  
NKA and NKB as the NK<sub>1</sub>, NK<sub>2</sub> and NK<sub>3</sub> receptors, respectively.

20 Evidence for the usefulness of tachykinin receptor antagonists in  
pain, headache, especially migraine, Alzheimer's disease, multiple  
sclerosis, attenuation of morphine withdrawal, cardiovascular changes,  
oedema, such as oedema caused by thermal injury, chronic inflammatory  
diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity  
25 and other respiratory diseases including allergic rhinitis, inflammatory  
diseases of the gut including ulcerative colitis and Crohn's disease, ocular  
injury and ocular inflammatory diseases, proliferative vitreoretinopathy,  
irritable bowel syndrome and disorders of bladder function including  
cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin  
30 Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R.

Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 5 1982 *Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, 10 *J. Med Chem.*, (1982) 25, 1009) and in arthritis [Levine *et al Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific 15 Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al, Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in 20 Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al, Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin 25 antagonists are believed to be useful are allergic conditions [Hamelet *et al, Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al, Science* (1988) 241, 1218-21 and Kimball *et al, J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al, PNAS* (1988) 85, 3235-9] and, possibly by 30 arresting or slowing  $\beta$ -amyloid-mediated neurodegenerative changes

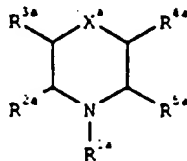
[Yankner *et al*, *Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al*, *Cancer Research* (1992) 52, 4554-7].

Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Lubner-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula

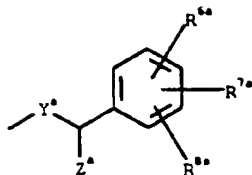


wherein R<sup>1a</sup> is a large variety of substituents;

- 4 -

$R^{2a}$  and  $R^{3a}$  are *inter alia* hydrogen;

$R^{4a}$  is *inter alia*



$R^{5a}$  is *inter alia* optionally substituted phenyl;

5  $R^{6a}$ ,  $R^{7a}$  and  $R^{8a}$  are a variety of substituents;

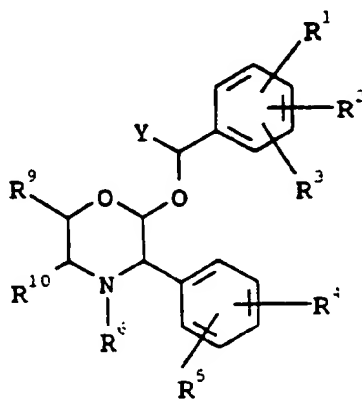
$X^a$  is O, S, SO or  $SO_2$ ;

$Y^a$  is *inter alia* O; and

$Z^a$  is hydrogen or  $C_{1-4}$ alkyl.

We have now found a further class of non-peptides which are potent  
10 antagonists of tachykinins, especially of substance P.

The present invention provides compounds of the formula (I):



(I)

15 wherein

$R^1$  represents hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-4}$ alkyl substituted by a hydroxy or  $C_{1-4}$ alkoxy group,  $OCF_3$ , hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN,  $SR^a$ ,  $SOR^a$ ,  $SO_2R^a$ ,  $COR^a$ ,  $CO_2R^a$  or  $CONR^aR^b$

20 where  $R^a$  and  $R^b$  are each independently hydrogen or  $C_{1-4}$ alkyl;

$R^2$  and  $R^3$  each independently represent hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy substituted by a  $C_{1-4}$ alkoxy group, or trifluoromethyl;

$R^4$  represents hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{2-6}$ alkenyl,  $C_{2-6}$ alkynyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl,  $C_{1-6}$ alkoxy,  $C_{1-4}$ alkyl substituted by a hydroxy or  $C_{1-4}$ alkoxy group,  $OCF_3$ , hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN,  $SR^a$ ,  $SOR^a$ ,  $SO_2R^a$ ,  $COR^a$ ,  $CO_2R^a$ ,  $CONR^aR^b$  where  $R^a$  and  $R^b$  are as previously defined;

$R^5$  represents hydrogen, halogen,  $C_{1-6}$ alkyl,  $C_{1-6}$ alkoxy substituted by a  $C_{1-4}$ alkoxy group, or trifluoromethyl;

$R^6$  represents  $C_{1-6}$ alkyl, optionally substituted by oxo, substituted by a 5-membered heteroaromatic ring selected from oxazole, thiazole, isoxazole, isothiazole, oxadiazole and thiadiazole, wherein each heteroaromatic ring is substituted at the available carbon atom by a group of the formula  $ZNR^7R^8$  where

$Z$  is  $C_{1-6}$ alkylene or  $C_{3-6}$ cycloalkyl;

$R^7$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by  $C_{1-4}$ alkoxy or hydroxyl;

$R^8$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by  $C_{1-4}$ alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or  $R^7$ ,  $R^8$  and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or  $C_{1-4}$ alkoxy optionally substituted by a  $C_{1-4}$ alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group  $S(O)$  or  $S(O)_2$  or a second nitrogen atom which will be part of a NH or  $NR^c$  moiety where  $R^c$  is  $C_{1-4}$ alkyl optionally substituted by hydroxy or  $C_{1-4}$ alkoxy;

or  $R^7$ ,  $R^8$  and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R<sup>7</sup> and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R<sup>9</sup> and R<sup>10</sup> each independently represent hydrogen or C<sub>1-4</sub>alkyl, or

5 R<sup>9</sup> and R<sup>10</sup> are joined so, together with the carbon atoms to which they are attached, there is formed a C<sub>5-7</sub> ring;

Y represents hydrogen or a C<sub>1-4</sub>alkyl group optionally substituted by a hydroxy group;

and pharmaceutically acceptable salts thereof.

10 Certain particularly apt compounds of the present invention include those wherein R<sup>1</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halogen or CF<sub>3</sub>.

Most aptly R<sup>2</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halogen or CF<sub>3</sub>.

Most aptly R<sup>3</sup> is hydrogen, fluorine, chlorine or CF<sub>3</sub>.

Favourably R<sup>1</sup> is fluorine, chlorine or CF<sub>3</sub>.

15 Favourably R<sup>2</sup> is hydrogen, fluorine, chlorine or CF<sub>3</sub>.

Favourably R<sup>3</sup> is hydrogen, fluorine, chlorine or CF<sub>3</sub>.

Preferably R<sup>1</sup> and R<sup>2</sup> are in the 3 and 5 positions of the phenyl ring.

More preferably, R<sup>1</sup> is 3-fluoro or 3-CF<sub>3</sub>.

More preferably, R<sup>2</sup> is 5-fluoro or 5-CF<sub>3</sub>.

20 More preferably, R<sup>3</sup> is hydrogen.

Most preferably, R<sup>1</sup> is 3-F or 3-CF<sub>3</sub>, R<sup>2</sup> is 5-F or 5-CF<sub>3</sub> and R<sup>3</sup> is hydrogen.

Most aptly R<sup>4</sup> is hydrogen.

Most aptly R<sup>5</sup> is hydrogen, fluorine, chlorine or CF<sub>3</sub>.

25 Preferably R<sup>4</sup> is hydrogen and R<sup>5</sup> is hydrogen or 4-fluoro.

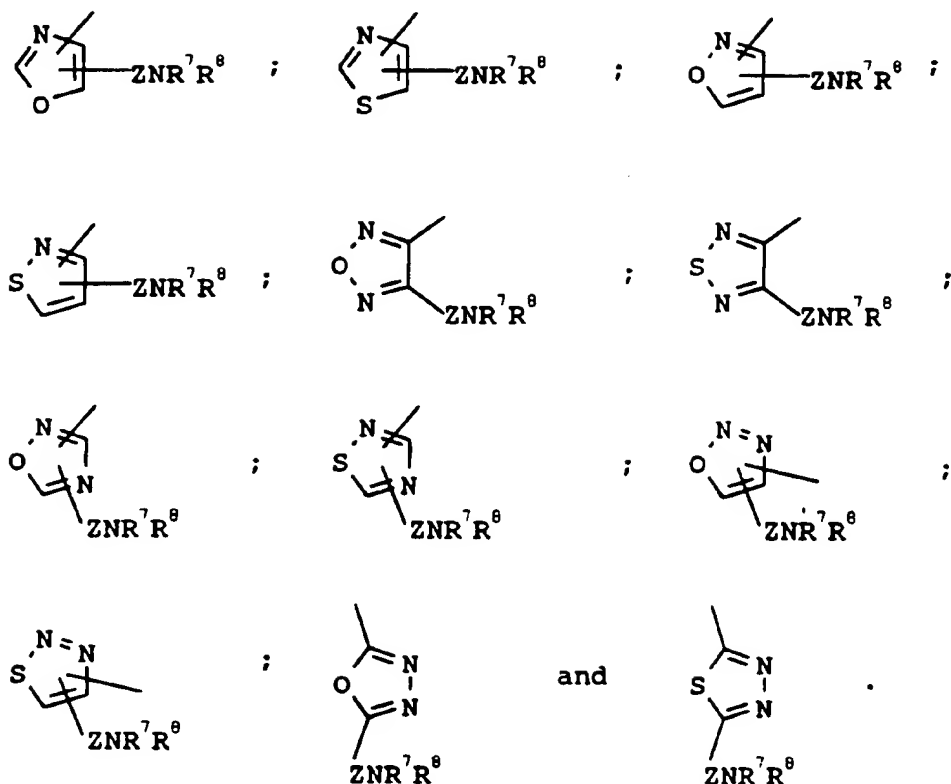
Most aptly R<sup>9</sup> and R<sup>10</sup> are each independently hydrogen or methyl.

Preferably R<sup>9</sup> is hydrogen. Preferably R<sup>10</sup> is hydrogen. Most preferably R<sup>9</sup> and R<sup>10</sup> are both hydrogen.

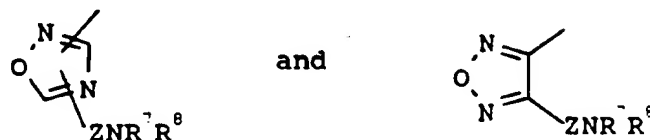
Favourably R<sup>6</sup> is C<sub>1-4</sub>alkyl, in particular CH<sub>2</sub>, CH(CH<sub>3</sub>) and CH<sub>2</sub>CH<sub>2</sub>

30 and especially CH<sub>2</sub>, substituted by a 5-membered ring selected from:





Particularly preferred heterocyclic rings are selected from:



5

With respect to compounds of the formula (I), Z may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and most favourably 1 or 2 carbon atoms. A particularly favourable group Z is  $\text{CH}_2$ .

10

With respect to compounds of the formula (I),  $\text{R}^7$  may aptly be a  $\text{C}_{1-4}$ alkyl group or a  $\text{C}_{2-4}$ alkyl group substituted by a hydroxyl or  $\text{C}_{1-2}$ alkoxy group,  $\text{R}^8$  may aptly be a  $\text{C}_{1-4}$ alkyl group or a  $\text{C}_{1-4}$ alkyl group substituted by a hydroxyl or  $\text{C}_{1-2}$ alkoxy group, or  $\text{R}^7$  and  $\text{R}^8$  may be linked so that,

together with the nitrogen atom to which they are attached, they form an azetidiny, pyrrolidiny, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C<sub>1-4</sub>alkyl group or a C<sub>2-4</sub>alkyl group substituted by a hydroxy or C<sub>1-2</sub>alkoxy group.

5       Where the group NR<sup>7</sup>R<sup>8</sup> represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR<sup>7</sup>R<sup>8</sup> represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably  
10   between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially  
15   5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R<sup>8</sup> represents a C<sub>2-4</sub>alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen  
20   containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR<sup>7</sup>R<sup>8</sup> include those wherein Z is CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub> and NR<sup>7</sup>R<sup>8</sup> is amino, methylamino, dimethylamino, diethylamino, azetidiny, pyrrolidino and morpholino.

25       Further preferred moieties represented by ZNR<sup>7</sup>R<sup>8</sup> are those wherein Z is CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub>, R<sup>7</sup> represents hydrogen, C<sub>1-4</sub>alkyl or C<sub>3-6</sub>cycloalkyl and R<sup>8</sup> is C<sub>2-4</sub>alkyl substituted by one or two substituents selected from hydroxy, C<sub>1-2</sub>alkoxy, azetidiny, pyrrolidino, piperidino, morpholino or thiomorpholino.

30       In particular, Z is preferably CH<sub>2</sub> and NR<sup>7</sup>R<sup>8</sup> is preferably dimethylamino, azetidiny or pyrrolidino, especially dimethylamino.

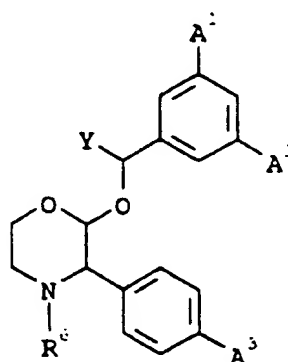
As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy,  
 5 n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part  
 10 of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

When used herein the term halogen means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of  
 15 which fluorine is preferred.

One favoured group of compounds of the present invention are of the formula (Ia):



(Ia)

20

wherein R<sup>6</sup> and Y are as defined in relation to formula (I) and

A<sup>1</sup> is fluorine or CF<sub>3</sub>;

A<sup>2</sup> is fluorine or CF<sub>3</sub>; and

A<sup>3</sup> is hydrogen or fluorine;  
and pharmaceutically acceptable salts thereof.

With respect to compounds of the formulae (I) and (Ia), Y may be  
aply a C<sub>1-4</sub>alkyl optionally substituted by a hydroxy group. In particular  
5 Y may be a methyl or hydroxymethyl group.

Specific compounds within the scope of this invention include:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-  
dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-  
phenylmorpholine;  
10 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-  
dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-(4-  
fluorophenyl)morpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-  
piperidinomethyl)-1,2,4-oxadiazol-5-yl)methylmorpholine;  
15 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(3-  
dimethylaminomethyl)-1,2,4-oxadiazol-5-yl)methyl-3-(S)-  
phenylmorpholine;  
and pharmaceutically acceptable salts thereof.

In a further aspect of the present invention, the compounds of  
20 formula (I) will preferably be prepared in the form of a pharmaceutically  
acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will  
be non-toxic pharmaceutically acceptable salts. Other salts may, however,  
be useful in the preparation of the compounds according to the invention  
25 or of their non-toxic pharmaceutically acceptable salts. Suitable  
pharmaceutically acceptable salts of the compounds of this invention  
include acid addition salts which may, for example, be formed by mixing a  
solution of the compound according to the invention with a solution of a  
pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid,  
30 p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid,  
tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of

amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

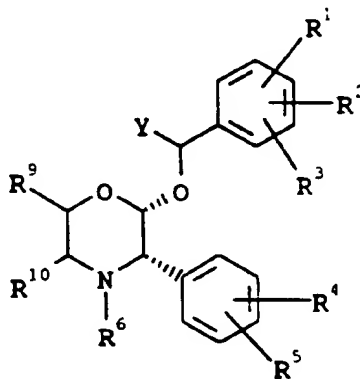
The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I) will have the preferred stereochemistry of the 2- and 3-position that is possessed by the compound of Example 1 (i.e. 2-(R), 3-(S)). Thus for example as shown in formula (Ib)



(Ib)

10

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

15 Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional  
20 tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the

present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into  
5 equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a  
10 dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to  
15 pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present  
20 invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for  
25 aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in  
30 association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the



nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease,

Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute  
5 dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives,  
10 sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delirium, withdrawal delirium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS  
15 and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid  
20 haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and  
25 peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for  
30 example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for

example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal  
5 cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive  
10 airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as  
15 poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

20 Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be  
25 of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or  
30 anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for

example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic,  
5 nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as  
10 rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and  
15 eosinophilic fasciitis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

20 The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such  
25 as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intracranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

30 Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl

5 sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used  
10 chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin  
15 and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-  
20 operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a  
25 twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT<sub>3</sub> antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as  
30 metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid,

such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of

respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a  $\beta_2$ -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D<sub>4</sub> antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT<sub>1</sub> agonists, especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and



an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low  
5 doses thereby minimising the risk of unwanted side effects.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

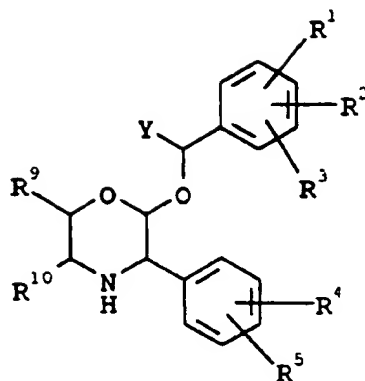
10 For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice  
15 per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day,  
20 preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and  
25 condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from compounds of formula (II)

- 24 -



(II)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^9$ ,  $R^{10}$  and  $Y$  are as defined in relation to formula (I) by reaction with a compound of formula (III):

5

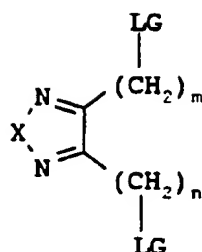


where  $R^{6a}$  is a group of the formula  $R^6$  as defined in relation to formula (I) or a precursor therefor and LG is a leaving group such as an alkyl- or  
 10 arylsulphonyloxy group (e.g. mesylate or tosylate) or a halogen atom (e.g. bromine, chlorine or iodine); and, if  $R^{6a}$  is a precursor group, converting it to a group  $R^6$  (in which process any reactive group may be protected and thereafter deprotected if desired).

This reaction may be performed in conventional manner, for  
 15 example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

Thus, for instance, where  $R^6$  is a  $C_{1-6}$ alkyl group substituted by a 1,2,5-oxadiazolyl or 1,2,5-thiadiazolyl group, each of which heteroaromatic rings is substituted by  $ZNR^7R^8$ , may be prepared by the reaction of a  
 20 compound of formula (II) with a compound of formula (IV)

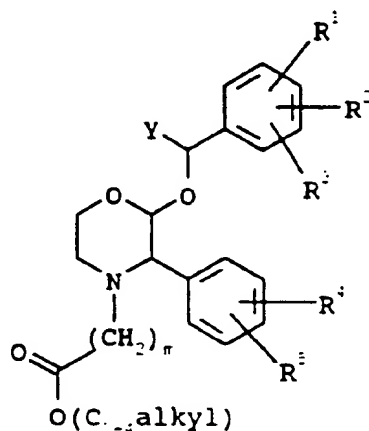
- 25 -



(IV)

where m is an integer from 1 to 6, n is an integer from 1 to 6, X is O or S  
 and each LG independently represents a leaving group as previously  
 5 defined, followed by reaction of the resultant compound with an amine of  
 formula  $\text{NHR}^7\text{R}^8$  to complete the group  $\text{ZNR}^7\text{R}^8$ .

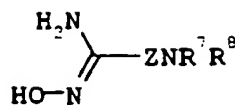
According to another process (B), compounds of formula (I) wherein  
 $\text{R}^6$  represents a  $\text{C}_{1-6}$ alkyl group substituted by a 1,2,4-oxadiazolyl or 1,2,4-  
 thiadiazolyl group, each of which heteroaromatic rings is substituted by  
 10  $\text{ZNR}^7\text{R}^8$ , may be prepared by reaction of a compound of formula (V):



(V)

wherein m is an integer from 1 to 6, with a compound of formula (VI):

- 26 -



(VI)

in the presence of a base.

Suitable bases of use in the reaction include alkali metals, such as,  
 5 for example, sodium, and alkali metal hydrides, such as, for example,  
 sodium hydride.

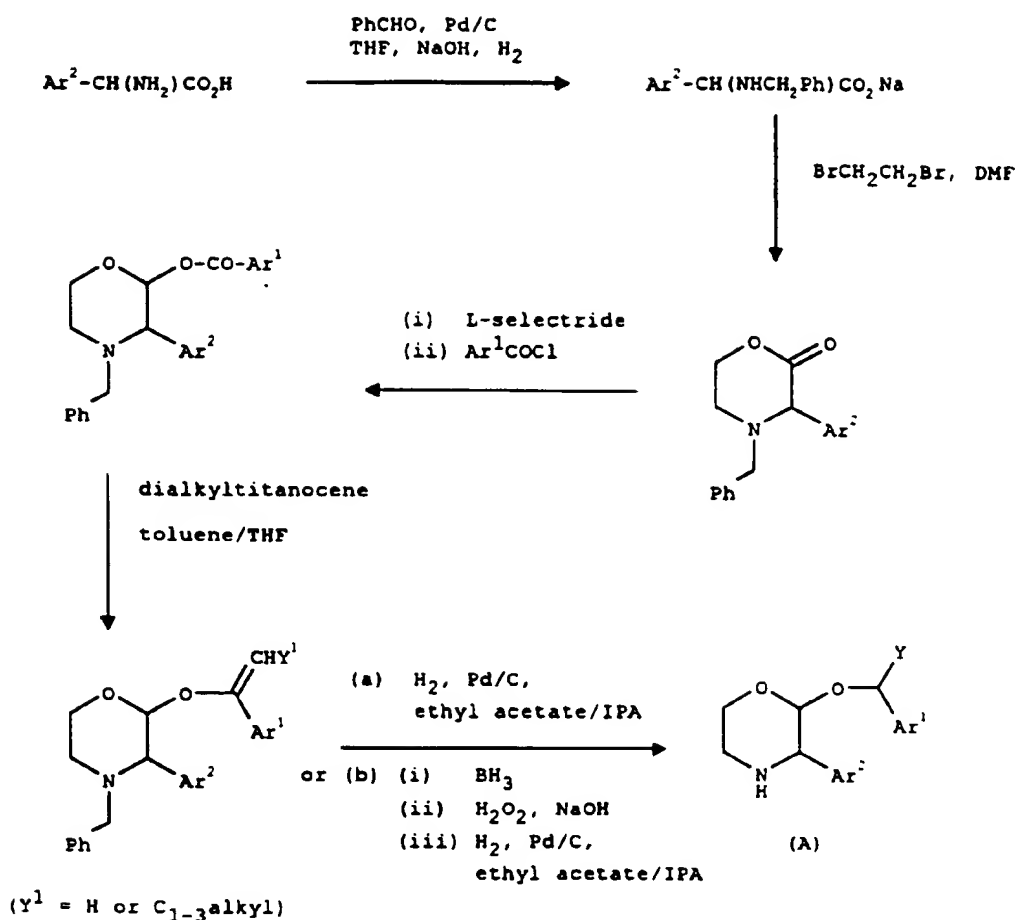
The reaction is conveniently effected in a suitable organic solvent.  
 Which solvents will be appropriate will depend on the nature of the base  
 used. For example, where the base used is an alkali metal, suitable  
 10 solvents will include alcohols, for example, ethanol, whereas where the  
 base used is an alkali hydride, suitable solvents will include ethers, for  
 example, tetrahydrofuran.

Preferably the reaction is conducted at elevated temperature, such  
 as the reflux temperature of the chosen solvent.

15 Compounds of formula (I) wherein  $\text{R}^6$  is  $\text{C}_{1-6}$ alkyl substituted by  
 thiazolyl may be prepared from compounds of formula (I) wherein  $\text{R}^6$  is  
 $\text{C}_{1-6}$ alkyl substituted by  $\text{CSNH}_2$  by reaction with a compound of formula  
 $\text{Hal}-\text{CH}_2\text{C}(\text{O})-\text{R}^{60}$ , where Hal is a halogen atom, such as bromine, chlorine  
 or iodine, and  $\text{R}^{60}$  represents H or a suitable substituent.

20 Intermediates of the formula (II) may be prepared as shown in the  
 following Scheme in which  $\text{Ar}^1$  represents the  $\text{R}^1, \text{R}^2, \text{R}^3$  substituted phenyl  
 group;  $\text{Ar}^2$  represents the  $\text{R}^4, \text{R}^5$  substituted phenyl group and Ph  
 represents phenyl:

- 27 -



L-Selectride is lithium tri-sec-butylborohydride.

The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the

5 skilled worker has read the disclosure herein:

- (i) D.A. Evans *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 4011.
- (ii) I. Yanagisawa *et al.*, *J. Med. Chem.*, (1984) 27, 849.
- (iii) R. Duschinsky *et al.*, *J. Am. Chem. Soc.*, (1948) 70, 657.
- (iv) F.N. Tebbe *et al.*, *J. Am. Chem. Soc.*, (1978) 100, 3611.
- 10 (v) N.A. Petasis *et al.*, *J. Am. Chem. Soc.*, (1990) 112, 6532.
- (vi) K. Takai *et al.*, *J. Org. Chem.*, (1987) 52, 4412.

Intermediates of formula (V) may be prepared by the reaction of a compound of formula (II) with a halogenated ester such as methyl bromoacetate. The reaction is conveniently effected in the presence of a

base such as an alkali metal carbonate, for example, potassium carbonate in a suitable anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at a temperature between 50°C and 150°C.

Intermediates of formula (VI) are either commercially available or  
5 may be prepared by conventional methodology. For example, by the reaction of a suitable acetonitrile derivative with hydroxyamine hydrochloride in an organic solvent such as ethanol, conveniently at room temperature.

Where they are not commercially available, the intermediates of  
10 formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the  
15 molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent  
20 stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds or, in the case of prodrugs, the parent  
25 compounds, were found to be active with  $IC_{50}$  at the  $NK_1$  receptor of less than  $1\mu M$  on said test method.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

DESCRIPTION 1(S)-(4-Fluorophenyl)glycineVia Chiral Synthesis:5 Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09g (33.0mmol) of 4-fluorophenylacetic acid in 100ml of anhydrous ether. The solution was cooled to -10°C and treated  
10 with 5.60ml (40.0mmol) of triethylamine followed by 4.30ml (35.0mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at -10°C for 40 minutes, then cooled to -78°C.

An oven-dried, 250ml round bottom flask, equipped with a septum  
15 and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31g (30.0mmol) of 4-(S)-benzyl-2-oxazolidinone in 40ml of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8ml of 1.6M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was added, via  
20 cannula, to the above mixture in the 3-necked flask. The cooling bath was removed from the resulting mixture and the temperature was allowed to rise to 0°C. The reaction was quenched with 100ml of saturated aqueous ammonium chloride solution, transferred to a 1l flask, and the ether and THF were removed *in vacuo*. The concentrated mixture was partitioned  
25 between 300ml of methylene chloride and 50ml of water and the layers were separated. The organic layer was washed with 100ml of 2N aqueous hydrochloric acid solution, 300ml of saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 400g of silica gel using 3:2 v/v  
30 hexanes/ether as the eluant afforded 8.95g of an oil that slowly solidified on standing. Recrystallisation from 10:1 hexanes/ether afforded 7.89g (83%) of the title compound as a white solid: mp 64-66°C. MS (FAB): m/z

314 ( $M^+ + H$ , 100%), 177 ( $M - ArCH_2CO + H$ , 85%).  $^1H$  NMR (400MHz,  $CDCl_3$ )  $\delta$  2.76 (1H, dd,  $J = 13.2, 9.2$ ), 3.26 (dd,  $J = 13.2, 3.2$ ), 4.16-4.34 (4H, m), 4.65 (1H, m), 7.02-7.33 (9H, m). Anal. Calcd for  $C_{18}H_{16}FNO_3$ ; C, 69.00; H, 5.15; N, 4.47; F, 6.06; Found: C, 68.86; H, 5.14; N, 4.48; F, 6.08.

5

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1l 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0ml of 1M potassium

- 10 bis(trimethylsilyl)amide solution in toluene and 85ml of THF and was cooled to  $-78^\circ C$ . An oven-dried 250ml round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20g (23.0mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Step A) in 40ml of THF. The acyl
- 15 oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below  $-70^\circ C$ . The acyl oxazolidinone flask was rinsed with 15ml of THF and the rinse was added,
- 20 via cannula, to the reaction mixture and the resulting mixture was stirred at  $-78^\circ C$  for 30 minutes. An oven-dried, 250ml round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89g (35.0mmol) of 2,4,6-trisopropylphenylsulfonyl azide in 40ml of THF. The azide solution was
- 25 stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal temperature of the mixture was maintained below  $-70^\circ C$ . After 2 minutes, the reaction was quenched with 6.0ml of glacial acetic acid, the cooling bath was removed and the mixture was stirred at room temperature for 18
- 30 hours. The quenched reaction mixture was partitioned between 300ml of ethyl acetate and 300ml of 50% saturated aqueous sodium bicarbonate



solution. The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 500g of silica gel using 2:1 v/v, then 1:1 v/v hexanes/methylene chloride as the eluant afforded 5.45g (67%) of the title compound as an oil. IR Spectrum (neat, 5  $\text{cm}^{-1}$ ): 2104, 1781, 1702.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  2.86 (1H, dd,  $J = 13.2, 9.6$ ), 3.40 (1H, dd,  $J = 13.2, 3.2$ ), 4.09-4.19 (2H, m), 4.62-4.68 (1H, m), 6.14 (1H, s), 7.07-7.47 (9H, m). Anal. Calcd. for  $\text{C}_{18}\text{H}_{15}\text{FN}_4\text{O}_3$ ; C 61.01; H, 4.27; N, 15.81; F, 5.36; Found: C, 60.99; H, 4.19; N, 15.80; F, 5.34.

10 Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40g (15.2mmol) of 3-((S)-azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone (from Step B) in 200ml of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28g (30.4mmol) of lithium hydroxide monohydrate was added in one portion and the resulting 15 mixture was stirred cold for 30 minutes. The reaction mixture was partitioned between 100ml of methylene chloride and 100ml of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2 x 100ml of methylene chloride and acidified to pH 2 with 2N aqueous hydrochloric acid solution. 20 The resulting mixture was extracted with 2 x 100ml of ethyl acetate; the extracts were combined, washed with 50ml of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 2.30g (77%) of the title compound as an oil that was used in the following step without further purification. IR Spectrum (neat, 25  $\text{cm}^{-1}$ ): 2111, 1724.  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  5.06 (1H, s), 7.08-7.45 (4H, m), 8.75 (1H, br s).

Step D: (S)-(4-Fluorophenyl)glycine

A mixture of 2.30g (11.8mmol) of (S)-azido-(4-fluorophenyl)acetic acid 30 (from Step C), 2.50mg 10% palladium on carbon catalyst and 160ml 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18

hours. The reaction mixture was filtered through Celite and the flask and filter cake were rinsed well with ~1l of 3:1 v/v water/acetic acid. The filtrate was concentrated *in vacuo* to about 50ml of volume. 300ml of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99g (100%) of the title compound. <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O+ NaOD) δ 3.97 (1H, s), 6.77 (2H, app t, J = 8.8), 7.01 (2H, app t, J = 5.6).

Via Resolution:

10 Step A' (4-Fluorophenyl)acetyl chloride

A solution of 150g (0.974mol) of 4-(fluorophenyl)acetic acid and 1ml of N,N-dimethylformamide in 500ml of toluene at 40°C was treated with 20ml of thionyl chloride and heated to 40°C. An additional 61.2ml of thionyl chloride was added dropwise over 1.5 hours. After the addition, the solution was heated at 50°C for 1 hour, the solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 150.4g (89.5%) of the title compound, bp = 68-70°C.

Step B': Methyl 2-bromo-3-(4-fluorophenyl)acetate

20 A mixture of 150.4g (0.872mol) of 4-(fluorophenyl)acetyl chloride (from Step A') and 174.5g (1.09mol) of bromine was irradiated at 40-50°C with a quartz lamp for 5 hours. The reaction mixture was added dropwise to 400ml of methanol and the solution was stirred for 16 hours. The solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 198.5g (92%) of the title compound, bp = 106-110°C.

Step C': Methyl (±)-(4-fluorophenyl)glycine

A solution of 24.7g (0.1mol) of methyl 2-bromo-2-(4-fluorophenyl)acetate (from Step B') and 2.28g (0.01mol) of benzyl triethylammonium chloride in 25ml of methanol was treated with 6.8g (0.105mol) of sodium azide and

- 33 -

the resulting mixture was stirred for 20 hours at room temperature. The reaction mixture was filtered; the filtrate was diluted with 50ml of methanol and hydrogenated in the presence of 0.5g of 10% Pd/C at 50 psi for 1 hour. The solution was filtered and the solvent removed *in vacuo*.

- 5 The residue was partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The organic phase was washed with water, saturated aqueous sodium chloride solution dried over magnesium sulfate and concentrated *in vacuo* to afford 9.8g of the title compound as an oil.

10 Step D': Methyl (S)-(4-fluorophenyl)glycinate

- A solution of 58.4g of methyl ( $\pm$ ) 4-(fluorophenyl)glycinate (from Step C') in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(+)-dibenzoyltartaric acid ((+)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to
- 15 age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 32.4g of methyl (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 93.2%). The mother liquors were concentrated *in vacuo* and the free base was liberated by partitioning between ethyl acetate and
- 20 aqueous sodium carbonate solution. A solution of free base, so obtained, in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(+)-dibenzoyltartaric acid ((+)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to
- 25 age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 47.0g of methyl (R)-(4-fluorophenyl)glycinate, (-)-DBT salt (ee = 75.8%). Recycling of the mother liquors and addition of (+)-DBT gave a second crop of 7.4g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee = 96.4%). The two crops of the (S)-amino ester (39.8g) were
- 30 combined in 200ml of 7:1 v/v ethanol/water, heated for 30 minutes and cooled to room temperature. Addition of ethyl acetate, cooling, and

filtration afforded 31.7g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee > 98%). Enantiomeric excess was determined by chiral HPLC (Crownpak CR(+) 5% MeOH in aq HClO<sub>4</sub> pH2 1.5ml/min 40°C 200nm).

A mixture of 17.5g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt  
5 and 32ml of 5.5N HCl (32ml) was heated at reflux for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 40ml of water. The aqueous solution was washed (3 x 30ml of ethyl acetate) and the layers were separated. The pH of the aqueous layer was adjusted to 7 using ammonium hydroxide and the precipitated solid was  
10 filtered to afford 7.4g of the title compound (ee = 98.8%).

## DESCRIPTION 2

### 4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

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#### Step A: N-Benzyl-(S)-(4-fluorophenyl)glycine

A solution of 1.87g (11.05mmol) of (S)-(4-fluorophenyl)-glycine (from Description 1) and 1.12ml (11.1mmol) of benzaldehyde in 11.1ml of 1N aqueous sodium hydroxide solution and 11ml of methanol at 0°C was  
20 treated with 165mg (4.4mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12ml (11.1mmol)) and sodium borohydride (165mg (4.4mmol)) were added to the reaction mixture and stirring was continued for 1.5hours. The reaction mixture was  
25 partitioned between 100ml of ether and 50ml of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2N aqueous hydrochloric acid solution and the solid that had precipitated was filtered, rinsed well with water, then ether, and dried to  
30 afford 1.95g of the title compound. <sup>1</sup>H NMR (400MHz, D<sub>2</sub>O + NaOD) δ 3.33 (2H, AB q, J = 8.4), 3.85 (1H, s), 6.79-7.16 (4H, m).

**Step B: 4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone**

A mixture of 1.95g (7.5mmol) of N-benzyl (S)-(4-fluorophenyl)glycine, 3.90ml (22.5mmol) of N,N-diisopropyl-ethylamine, 6.50ml (75.0mmol) of 1,2-dibromoethane and 40ml of N,N-dimethylformamide was stirred at 100°C for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated *in vacuo*. The residue was partitioned between 250ml of ether and 100ml of 0.5N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100ml of saturated aqueous sodium bicarbonate solution, 3 x 150ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 125g of silica gel using 3:1 v/v hexanes/ether as the eluant afforded 1.58g (74%) of the title compound as an oil. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 2.65 (1H, dt, J = 3.2, 12.8), 3.00 (1H, dt, J = 12.8, 2.8), 3.16 (1H, d, J = 13.6), 3.76 (1H, d, J = 13.6), 4.24 (1H, s), 4.37 (1H, dt, J = 13.2, 3.2), 4.54 (1H, dt, J = 2.8, 13.2), 7.07-7.56 (9H, m).

20

**DESCRIPTION 3****4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)morpholine**

A solution of 2.67g (10.0mmol) of 4-benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone (Description 2) in 40ml of dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml (20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between

300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>) δ 2.50 (1H, dt, J = 3.4, 12.0), 2.97 (1H, app d, J = 12.0), 2.99 (1H, d, J = 13.6), 3.72-3.79 (1H, m), 3.82 (1H, d, J = 2.6), 4.00 (1H, d, J = 13.6), 4.20 (dt, J = 2.4, 11.6), 6.22 (1H, d, J = 2.6), 7.22-7.37 (7H, m), 7.57 (2H, app d, J = 6.8), 8.07 (1H, s), 8.47 (2H, s). MS (FAB) m/z 528 (M+H, 25%), 270 (100%). Anal. Calcd for C<sub>26</sub>H<sub>20</sub>F<sub>7</sub>NO<sub>3</sub>: C, 59.21; H, 3.82; N, 2.66; F, 25.21. Found: C, 59.06; H, 4.05; N, 2.50; F, 25.18.

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#### DESCRIPTION 4

##### 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyl)oxy)-3-(S)-(4-fluorophenyl)morpholine

##### 20 Step A: Dimethyl titanocene

A solution of 2.49g (10.0mmol) of titanocene dichloride in 50ml of ether in the dark at 0°C was treated with 17.5ml of 1.4M methyllithium solution in ether maintaining the internal temperature below 5°C. The resulting yellow/orange mixture was stirred at room temperature for 30 minutes and the reaction was quenched by slowly adding 25g of ice. The quenched reaction mixture was diluted with 50ml of ether and 25ml of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 2.03g (98%) of the title compound as a light-sensitive solid. The dimethyl titanocene could be stored as a solution in toluene at 0°C for at least 2 weeks without

apparent chemical degradation.  $^1\text{H}$  NMR (200MHz,  $\text{CDCl}_3$ )  $\delta$  -0.15 (6H, s), 6.06 (10H, s).

Step B: 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of the compound of Description 3 (2.50g, 4.9mmol) and 2.50g (12.0mmol) of dimethyl titanocene (from Step A) in 35ml of 11 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. An analytical sample was obtained via recrystallisation from isopropanol:  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  2.42 (1H, dt,  $J$  = 3.6, 12.0), 2.90 (1H, app d,  $J$  = 12.0), 2.91 (1H, d,  $J$  = 13.6), 3.62-3.66 (1H, m), 3.72 (1H, d,  $J$  = 2.6), 3.94 (1H, d,  $J$  = 13.6), 4.09 (1H, dt,  $J$  = 2.4, 12.0), 4.75 (1H, d,  $J$  = 3.2), 4.82 (1H, d,  $J$  = 3.2), 5.32 (1H, d,  $J$  = 2.6), 7.09 (2H, t,  $J$  = 8.8), 7.24-7.33 (5H, m), 7.58-7.62 (2H, m), 7.80 (1H, s), 7.90 (2H, s); MS (FAB) 526 (M+H, 75%), 270 (100%). Anal. Calcd for  $\text{C}_{27}\text{H}_{22}\text{F}_7\text{NO}_2$ : C, 61.72; H, 4.22; N, 2.67; F, 25.31. Found: C, 61.79; H, 4.10; N, 2.65; F, 25.27%.

20

DESCRIPTION 5

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 4 (4.0g) was dissolved in ethyl acetate (50ml) and isopropanol (16ml). To this solution was added palladium on charcoal (1.5g) and the mixture was hydrogenated at 40 psi for 36h. The catalyst was removed by filtration through Celite and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica using 100% ethyl acetate and then 1-10% methanol in ethyl acetate. This afforded isomer A 500mg (15%) and isomer B 2.6g (80%) as clear oils -

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isomer B crystallised on standing. For the title compound:  $^1\text{H}$  NMR (400MHz,  $\text{CDCl}_3$ )  $\delta$  1.16 (3H, d,  $J = 6.8\text{MHz}$ ), 1.80 (1H, br s), 3.13 (1H, dd,  $J = 3.2, 12.4\text{Hz}$ ), 3.23 (1H, dt,  $J = 3.6, 12.4\text{Hz}$ ), 3.63 (1H, dd,  $J = 2.4, 11.2\text{Hz}$ ), 4.01 (1H, d,  $J = 2.4\text{Hz}$ ), 4.13 (1H, dt,  $J = 3.2, 12.0\text{Hz}$ ), 4.42 (1H, d,  $J = 2.4\text{Hz}$ ), 4.19 (1H, q,  $J = 6.8\text{Hz}$ ), 7.04-7.09 (2H, m), 7.27-7.40 (4H, m), 7.73 (1H, s); MS (FAB) 438 (M+H, 75%), 180 (100%).

HCl salt formation. To a solution of the free base (0.77g) in diethyl ether (10ml) was added 1M-HCl in methanol (1.75ml). The solution was evaporated to dryness and on addition of diethyl ether crystals formed. The solution was filtered and the residue washed with diethyl ether to give the title compound hydrochloride salt mp 248-250°C. Found: C, 50.46; H, 3.85; N, 3.01; Cl, 7.31.  $\text{C}_{20}\text{H}_{18}\text{F}_7\text{NO}_2\cdot\text{HCl}$  requires C, 50.70; H, 4.04; N, 2.96; Cl, 7.48%.

#### DESCRIPTION 6

##### 4-Benzyl-3-(S)-phenyl-2-morpholinone

##### Step A: N-Benzyl-(S)-phenylglycine

A solution of 1.51g (10.0mmol) of (S)-phenylglycine in 5ml of 2N aqueous sodium hydroxide solution was treated with 1.0ml (10.0mmol) of benzaldehyde and stirred at room temperature for 20 minutes. The solution was diluted with 5ml of methanol, cooled to 0°C, and carefully treated with 200mg (5.3mmol) of sodium borohydride. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with 20ml of water and extracted with 2 x 25ml of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid to pH 6 and the solid that precipitated was filtered, washed with 50ml of water, 50ml of 1:1 v/v methanol/ethyl ether and 50ml of ether, and dried to afford 1.83g (76%) of product, mp 230-



232°C. Anal. Calcd for C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub>: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.17; H, 6.19; N, 5.86.

**Step B: 4-Benzyl-3-(S)-phenyl-2-morpholinone**

5 A mixture of 4.00g (16.6mmol) of N-benzyl-(S)-phenylglycine (from Step A) 5.00g (36.0mmol) of potassium carbonate, 10.0ml of 1,2-dibromoethane and 25ml of N,N-dimethylformamide was stirred at 100°C for 20 hours. The mixture was cooled and partitioned between 200ml of ethyl ether and 100ml of water. The layers were separated and the organic layer was  
10 washed with 3 x 50ml of water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on 125g of silica gel eluting with 9:1 v/v, then 4:1 hexanes/ethyl ether to afford 2.41g (54%) of the product as a solid, mp 98-100°C. <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 2.54-2.68 (1H, m), 2.96 (1H, dt, J = 12.8, 2.8), 3.14  
15 (1H, d, J = 13.3), 3.75 (1H, d, J = 13.3), 4.23 (1H, s), 4.29-4.37 (1H, m), 4.53 (dt, J = 3.2, 11.0), 7.20-7.56 (10H, m). MS (FAB): m/z 268 (M+H; 100%). Anal. Calcd for C<sub>17</sub>H<sub>17</sub>NO<sub>2</sub>: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.06; H, 6.40; N, 5.78.

20

**DESCRIPTION 7**

**4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-phenylmorpholine**

A solution of 2.67g (10.0mmol) of the compound of Description 6 in 40ml of  
25 dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml (20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was  
30 stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture

was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined  
5 organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. <sup>1</sup>H NMR (200MHz ppm, CDCl<sub>3</sub>) δ 2.50 (1H, dt, J = 3.4, 12.0), 2.97 (1H, app d, J = 12.0), 2.99 (1H, d, J = 13.6), 3.72-3.79 (1H, m), 3.82 (1H, d, J = 2.6), 4.00 (1H, d, J = 13.6), 4.20 (dt, J =  
10 2.4, 11.6), 6.22 (1H, d, J = 2.6), 7.22-7.37 (7H, m), 7.57 (2H, appd, J = 6.8), 8.07 (1H, s), 8.47 (2H, s). Anal. Calcd for C<sub>26</sub>H<sub>21</sub>F<sub>6</sub>NO<sub>3</sub>: C, 61.29; H, 4.16; N, 2.75; F, 22.38. Found: C, 61.18; H, 4.14; N, 2.70; F, 22.13.

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#### DESCRIPTION 8

##### 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-phenylmorpholine

A solution of 2.50g (4.9mmol) of the compound of Description 7 and 2.50g (12.0mmol) of dimethyl titanocene (Description 4a), in 35ml of 1:1 v/v  
20 THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 2.42 (1H, dt, J = 3.6, 12.0), 2.89 (app d, J = 11.6), 2.92 (1H, d, J =  
25 13.6), 3.61-3.66 (1H, m), 3.73 (1H, d, J = 2.8), 4.00 (1H, d, J = 13.6), 4.09 (1H, dt, J = 2.4, 11.6), 4.75 (1H, d, J = 2.8), 4.79 (1H, d, J = 2.8), 5.36 (1H, d, J = 2.4), 7.23-7.41 (7H, m), 7.63 (1H, app d, J = 7.2), 7.79 (1H, s), 7.91 (2H, s). MS (FAB) m/z 508 (M+1, 25%). Anal. Calcd. for C<sub>27</sub>H<sub>23</sub>F<sub>6</sub>NO<sub>2</sub>: C, 63.90; H, 4.57; N, 2.76; F, 22.46. Found: C, 63.71; H, 4.53; N, 2.68; F,  
30 22.66.

DESCRIPTION 92-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenylmorpholine

A mixture of the compound of Description 8 (1.5g) and 10% palladium on carbon catalyst (750mg) in a mixture of isopropanol/ethyl acetate (25ml, 3:2 v/v) was stirred under an atmosphere of hydrogen for 48h. The catalyst was removed by filtration through celite and the reaction flask and filter pad were rinsed with ethyl acetate (500ml). The filtrate was concentrated *in vacuo*, flash chromatography afforded epimer A (106mg) and epimer B (899mg) as clear oils. The title compound, epimer B had the following analysis: <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ 1.46 (3H, d, J = 6.8Hz), 1.92 (1H, brs), 3.13 (1H, dd, J = 3.0, 12.6Hz), 3.24 (1H, dt, J = 3.6, 12.6Hz), 3.62 (1H, dd, J = 3.6, 11.2Hz), 4.04 (1H, d, J = 2.4Hz), 4.14 (1H, dt, J = 3.0, 11.2Hz), 4.48 (1H, d, J = 2.4Hz), 4.90 (1H, q, J = 6.8Hz), 7.21-7.32 (7H, m), 7.64 (1H, s). MS (CI<sup>+</sup>) m/z 420 (M<sup>+</sup>+1, 20%), 178 (100%). Anal. Calcd. for C<sub>20</sub>H<sub>19</sub>F<sub>6</sub>NO<sub>2</sub>: C, 57.28; H, 4.57; N, 3.34; F, 27.18. Found: C, 57.41; H, 4.61; N, 3.29; F, 27.23.

EXAMPLE 12-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-(dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-phenylmorpholinea) 3,4-Dimethyl-1,2,5-oxadiazole

A mixture of succinic anhydride (20g) and dimethyl glyoxime (23.2g) were heated in a 3-necked round bottom flask equipped with distillation apparatus. At 100°C the reaction mixture liquified, and at 150°C the product distilled. A second distillation yielded the product as a colourless liquid: bp 154-159°C. <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 2.35 (6H, s).

b) 3-Chloromethyl-4-methyl-1,2,5-oxadiazole

$\alpha,\alpha^1$ -Azoisobutyronitrile (0.4g) was added to the compound described in (a) (12.7g) and sulfonyl chloride (10.41ml) was added portionwise. The mixture was heated at 90°C for 3½ hours. Vacuum  
5 distillation (8mm Hg) yielded the product as a colourless liquid bp 60°C (8mm Hg). <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta$  2.48 (3H, s), 4.72 (2H, s).

c) 3,4-Bis(chloromethyl)-1,2,5-oxadiazole

$\alpha,\alpha^1$ -Azoisobutyronitrile (0.2g) was added to the compound described in (b) (3.27g) and sulfonyl chloride (2ml) was added portionwise.  
10 The mixture was heated at 90°C for 4 hours. The mixture was cooled, diluted with water (20ml), and extracted with ether (3x10ml). The combined organic phases were washed with brine (50ml), dried (MgSO<sub>4</sub>), and concentrated to leave a pale yellow oil, which was a mixture of the  
15 starting material and product. <sup>1</sup>H NMR signals for the product are as follows: <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta$  2.48 (3H, s), 4.72 (2H, s), 4.85 (4H, s).

d) 2-(R)-(1(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-(dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-phenylmorpholine  
20

The compound of Description 9 (300mg) in dimethylformamide (2ml) was added slowly to a stirred mixture of the compound described in (c) (220mg) and potassium carbonate (273mg) in dimethylformamide (2ml) at room temperature. The mixture was then heated at 60°C for 4 hours,  
25 and then cooled. Dimethylamine (2ml) was added to the mixture, and stirred at room temperature for 4 hours. The reaction mixture was diluted with water (50ml) and extracted with ethyl acetate (3x30ml). The combined organic phases were washed with brine (1x50ml), dried (MgSO<sub>4</sub>), and concentrated to leave an oil. This was purified by  
30 chromatography on silica using ethyl acetate in hexane (1:4) as eluant to afford the title compound as an oil. <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>)  $\delta$  1.46 (3H,

d, J=6.6Hz), 2.19 (6H, s), 2.68 (1H, td, J=3.3Hz, 11.7Hz), 2.88 (1H, d, J=11.8Hz), 3.38 (1H, d, J=14Hz), 3.48 (1H, d, J=14.5Hz), 3.49 (1H, d, J=2.8Hz), 3.60 (1H, d, J=14Hz), 3.65 (1H, m), 3.87 (1H, d, J=14.5Hz), 4.25 (1H, td, J=2.5Hz, J=11.4Hz), 4.36 (1H, d, J=3.6Hz), 4.86 (1H, q, J=6.7Hz),  
5 7.16 (2H, s), 7.33 (3H, m), 7.43 (2H, broad s), 7.61 (1H, s) MS (ES) m/z 559 (MH<sup>+</sup>).

### EXAMPLE 2

10 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

This compound was prepared according to the procedure described in Example 1 using the compound of Description 5 as starting material.

15 Purification by chromatography on silica using ethyl acetate in hexane (1:9, 1:3, then 1:1) as eluant afforded the title compound as a colourless oil. <sup>1</sup>H NMR (360MHz, DMSO) δ 1.39 (3H, d, J=6.6Hz), 2.18 (6H, s), 2.38 (1H, d, J=6.3Hz) 2.52 (1H, td, J=3.4Hz, 11.8Hz), 2.83 (1H, d, J=11.4Hz), 3.30 (1H, d, J=8.4Hz), 3.42 (2H, d, J=14.1Hz), 3.58 (1H, m), 3.78 (1H, d, J=14.7Hz), 4.13 (1H, t, J=9.2Hz), 4.34 (1H, d, J=2.7Hz), 4.96 (1H, d, J=6.6Hz), 7.13 (2H, t, J=8.9Hz), 7.42 (2H, s), 7.52 (2H, t, J=6.2Hz), 7.86 (1H, s). MS (ES) m/z 577 (MH<sup>+</sup>).

### 25 EXAMPLE 3

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-piperidinomethyl-1,2,4-oxadiazol-5-yl)methylmorpholine

(a) 2-(R)-(1-(R)-(3,5-Bistrifluoromethyl)phenyl)ethoxy)-4-carbomethoxymethyl-3-(S)-phenylmorpholine  
30

Methyl bromoacetate (0.15ml) was added to a stirred mixture of the compound of Description 9 (0.6g) and potassium carbonate (0.52g) in dry dimethylformamide at 60°C. After 15 mins the reaction mixture was diluted with water (100ml). The aqueous phase was washed with ethyl acetate (3x25ml). The combined organic phase was washed with brine, dried (MgSO<sub>4</sub>) and concentrated to afford a clear oil. Purification was carried out by chromatography on silica eluting with 20% ethyl acetate in petrol to afford a clear oil (0.592g). <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.46 (1H, d, J=10Hz), 2.88-3.03 (2H, m), 3.08 (1H, d, J=12Hz), 3.33 (1H, d, J=12Hz), 3.61 (3H, s), 3.62 (1H, m), 3.90 (1H, m), 4.28-4.42 (2H, m), 4.86 (1H, q, J=10Hz), 7.15 (2H, s), 7.26-7.42 (5H, m), 7.60 (1H, s). MS (CI<sup>+</sup>) m/z 492 (M+1<sup>+</sup>, 100%).

(b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-piperidinomethyl-1,2,4-oxadiazol-5-yl)methylmorpholine

Sodium hydride (0.057g) and 2-(1-piperidino)acetamidoxime (0.188g) were stirred together with molecular sieves and dry tetrahydrofuran for ½ hr. A solution of the ester (Step a) in tetrahydrofuran was added dropwise to this solution over 3 mins. The reaction was heated at reflux for ½ hr. The molecular sieves were filtered and washed with ethyl acetate. The filtrate was evaporated under reduced pressure and the residue dispersed between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3x25ml). The combined organics were washed with brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure to afford a brown oil. Purification by chromatography on flash silica using 50/50 ethyl acetate/petrol as eluant afforded the title compound as a clear oil. <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.36-1.66 (9H, m), 2.43-2.54 (4H, m), 2.68-2.82 (1H, m), 2.96-3.06 (1H, m), 3.60-3.76 (5H, m), 3.96 (1H, d, J= 2.2Hz), 2.46-4.40 (2H, m), 4.82-4.90 (1H, q), 7.14 (2H, s), 7.30-7.48 (5H, m), 7.60 (1H, s). MS CI<sup>+</sup> m/z 599 (M+1<sup>+</sup>, 100%).

EXAMPLE 4

5 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(3-(N,N-  
dimethylaminomethyl)-1,2,4-oxadiazol-5-yl)methyl-3-(S)-  
phenylmorpholine

(a) (N,N-Dimethylamino)acetamide oxime

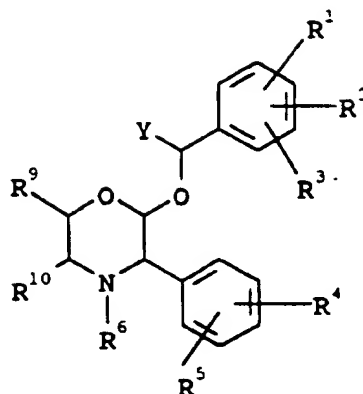
Dimethylaminoacetonitrile (5g) was dissolved in ethanol (12ml).  
10 Hydroxylamine hydrochloride (4.13g) was dissolved in water (5ml) and  
added to the reaction mixture over 3 min resulting in a slightly exothermic  
reaction. The mixture was cooled and sodium carbonate was added  
portionwise and the reaction mixture was stirred for 1hr. The mixture  
was filtered and concentrated *in vacuo* to afford a viscous white oil. This  
15 was crystallised from hot ethanol. (3.45g): mp 135°C.  
<sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 2.69 (6H, s), 3.60 (2H, s), 6.06 (2H, s).

(b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(3-(N,N-  
dimethylaminomethyl)-1,2,4-oxadiazol-5-yl)methyl-3-(S)-  
20 phenylmorpholine

The compound of Example 3a was reacted with the product of step  
(a) above according to the procedure described for Example 3b to afford the  
title compound. (250MHz, CDCl<sub>3</sub>) δ 1.39 (3H, d, J=7Hz), 2.29 (6H, s), 2.58-  
2.72 (1H, m), 2.90-2.98 (1H, br d), 3.53-3.64 (5H, m), 3.85 (1H, d, J=15Hz),  
25 4.18-4.31 (1H, m), 4.74-4.85 (1H, q, J=7Hz), 6.93-7.08 (4H, m), 7.32-7.42  
(2H, m), 7.56 (1H, s). MS CI<sup>+</sup> m/z 577 (M+1<sup>+</sup>, 100%).

**CLAIMS:**

1. A compound of the formula (I):



(I)

wherein

R<sup>1</sup> represents hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-4</sub>alkyl substituted by a hydroxy or C<sub>1-4</sub>alkoxy group, OCF<sub>3</sub>, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR<sup>a</sup>, SOR<sup>a</sup>, SO<sub>2</sub>R<sup>a</sup>, COR<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup> or CONR<sup>a</sup>R<sup>b</sup> where R<sup>a</sup> and R<sup>b</sup> are each independently hydrogen or C<sub>1-4</sub>alkyl;

R<sup>2</sup> and R<sup>3</sup> each independently represent hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy substituted by a C<sub>1-4</sub>alkoxy group, or trifluoromethyl;

R<sup>4</sup> represents hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>2-6</sub>alkenyl, C<sub>2-6</sub>alkynyl, C<sub>3-7</sub>cycloalkyl, C<sub>3-7</sub>cycloalkylC<sub>1-4</sub>alkyl, C<sub>1-6</sub>alkoxy, C<sub>1-4</sub>alkyl substituted by a hydroxy or C<sub>1-4</sub>alkoxy group, OCF<sub>3</sub>, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR<sup>a</sup>, SOR<sup>a</sup>, SO<sub>2</sub>R<sup>a</sup>, COR<sup>a</sup>, CO<sub>2</sub>R<sup>a</sup>, CONR<sup>a</sup>R<sup>b</sup> where R<sup>a</sup> and R<sup>b</sup> are as previously defined;

R<sup>5</sup> represents hydrogen, halogen, C<sub>1-6</sub>alkyl, C<sub>1-6</sub>alkoxy substituted by a C<sub>1-4</sub>alkoxy group, or trifluoromethyl;

R<sup>6</sup> represents C<sub>1-6</sub>alkyl, optionally substituted by oxo, substituted by a 5-membered heteroaromatic ring selected from oxazole, thiazole,



isoxazole, isothiazole, oxadiazole and thiadiazole, wherein each heteroaromatic ring is substituted at the available carbon atom by a group of the formula  $ZNR^7R^8$  where

Z is  $C_{1-6}$ alkylene or  $C_{3-6}$ cycloalkyl;

5  $R^7$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by  $C_{1-4}$ alkoxy or hydroxyl;

$R^8$  is hydrogen or  $C_{1-4}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{3-7}$ cycloalkyl $C_{1-4}$ alkyl, or  $C_{2-4}$ alkyl substituted by  $C_{1-4}$ alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms  
10 selected from N, O and S;

or  $R^7$ ,  $R^8$  and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or  $C_{1-4}$ alkoxy optionally substituted by a  $C_{1-4}$ alkoxy or hydroxyl group, and optionally containing a double bond,  
15 which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)<sub>2</sub> or a second nitrogen atom which will be part of a NH or NR<sup>c</sup> moiety where R<sup>c</sup> is  $C_{1-4}$ alkyl optionally substituted by hydroxy or  $C_{1-4}$ alkoxy;

or  $R^7$ ,  $R^8$  and the nitrogen atom to which they are attached form a  
20 non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

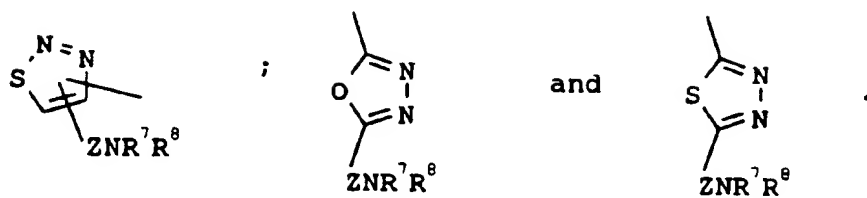
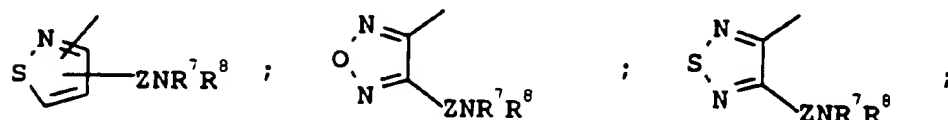
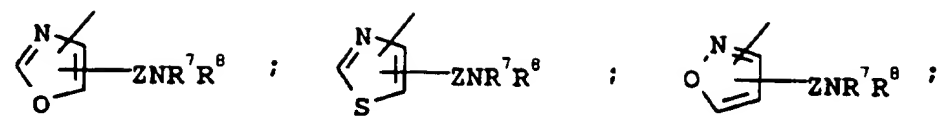
or Z,  $R^7$  and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

$R^9$  and  $R^{10}$  each independently represent hydrogen or  $C_{1-4}$ alkyl, or  
25  $R^9$  and  $R^{10}$  are joined so, together with the carbon atoms to which they are attached, there is formed a  $C_{3-7}$  ring;

Y represents hydrogen or a  $C_{1-4}$ alkyl group optionally substituted by a hydroxy group;

or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1 wherein R<sup>1</sup> is hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halogen or CF<sub>3</sub>.
3. A compound as claimed in claim 1 or claim 2 wherein R<sup>2</sup> is  
5 hydrogen, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, halogen or CF<sub>3</sub>.
4. A compound as claimed in any one of claims 1 to 3 wherein R<sup>3</sup> is hydrogen, fluorine, chlorine or CF<sub>3</sub>.
- 10 5. A compound as claimed in any one of claims 1 to 4 wherein R<sup>1</sup> and R<sup>2</sup> are in the 3 and 5 positions of the phenyl ring.
6. A compound as claimed in any one of claims 1 to 5 wherein R<sup>4</sup> is hydrogen and R<sup>5</sup> is hydrogen or 4-fluoro.  
15
7. A compound as claimed in any one of claims 1 to 6 wherein R<sup>9</sup> and R<sup>10</sup> are each independently hydrogen or methyl.
8. A compound as claimed in any one of claims 1 to 7 wherein R<sup>6</sup>  
20 is C<sub>1-6</sub>alkyl substituted by a 5-membered ring selected from:



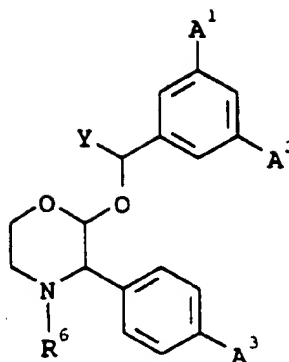
9. A compound as claimed in claim 8 wherein the 5-membered  
5 ring is selected from:



10. A compound as claimed in any one of claims 1 to 9 wherein Z  
10 is CH<sub>2</sub> or CH<sub>2</sub>CH<sub>2</sub> and NR<sup>7</sup>R<sup>8</sup> is amino, methylamino, dimethylamino,  
diethylamino, azetidiny, pyrrolidino and morpholino.

11. A compound of the formula (Ia):

- 50 -



(Ia)

wherein R<sup>6</sup> and Y are as defined in claim 1 and

A<sup>1</sup> is fluorine or CF<sub>3</sub>;

5 A<sup>2</sup> is fluorine or CF<sub>3</sub>; and

A<sup>3</sup> is hydrogen or fluorine;

or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in any one of claims 1 to 11 wherein  
10 Y is C<sub>1-4</sub>alkyl optionally substituted by a hydroxy group.

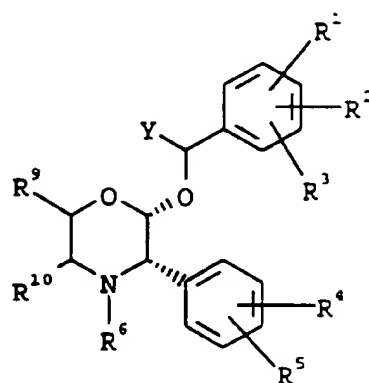
13. A compound selected from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-  
dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-  
15 phenylmorpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(4-  
dimethylaminomethyl)-1,2,5-oxadiazol-3-yl)methyl-3-(S)-(4-  
fluorophenyl)morpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(3-  
20 piperidinomethyl)-1,2,4-oxadiazol-5-yl)methylmorpholine;  
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(3-  
dimethylaminomethyl)-1,2,4-oxadiazol-5-yl)methyl-3-(S)-  
phenylmorpholine;

or a pharmaceutically acceptable salt thereof.

14. A compound as claimed in any one of claims 1 to 12 which has the stereochemistry of the 2- and 3-position that is shown in formula

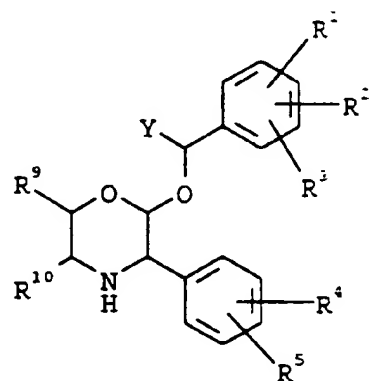
5 (Ib)



(Ib)

10 15. A process for the preparation of a compound as claimed in any one of claims 1 to 14, which comprises:

(A), reacting a compound of formula (II)



(II)

wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$ ,  $R^9$ ,  $R^{10}$  and Y are as defined in claim 1 with a compound of formula (III):

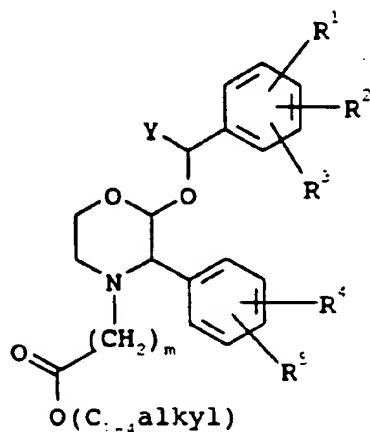


5

where  $R^{6*}$  is a group of the formula  $R^6$  as defined in claim 1 or a precursor therefor and LG is a leaving group such as an alkyl- or arylsulphonyloxy group or a halogen atom; and, if  $R^{6*}$  is a precursor group, converting it to a group  $R^6$ ; or

10

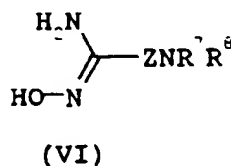
(B), where  $R^6$  represents a  $C_{1-6}$ alkyl group substituted by a 1,2,4-oxadiazolyl or 1,2,4-thiadiazolyl group, each of which heteroaromatic rings is substituted by  $ZNR^7R^8$ , by reaction of a compound of formula (V):



(V)

15

wherein m is an integer from 1 to 6, with a compound of formula (VI):



(VI)

20 in the presence of a base;

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to  
5 obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt thereof.

16. A compound as claimed in any one of claims 1 to 14 for use in  
10 therapy.

17. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 14 in association with a pharmaceutically acceptable carrier or excipient.

15

18. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1, or a  
20 pharmaceutically acceptable salt thereof, or a composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

19. A method according to claim 18 where the physiological  
25 disorder is pain or inflammation.

20. A method according to claim 18 where the physiological disorder is migraine.

21. A method according to claim 18 where the physiological  
30 disorder is emesis.

22. A method according to claim 18 where the physiological disorder is postherpetic neuralgia.

23. The use of a compound as claimed in any one of claims 1 to 14  
5 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

24. The use of a compound as claimed in any one of claims 1 to 14  
10 for the manufacture of a medicament for the treatment or prevention of pain or inflammation.

25. The use of a compound as claimed in any one of claims 1 to 14  
15 for the manufacture of a medicament for the treatment or prevention of migraine.

26. The use of a compound as claimed in any one of claims 1 to 14  
for the manufacture of a medicament for the treatment or prevention of emesis.

20 27. The use of a compound as claimed in any one of claims 1 to 14 for the manufacture of a medicament for the treatment or prevention of postherpetic neuralgia.



## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/GB 96/00587

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D413/06 C07D417/06 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 577 394 (MERCK & CO. INC.) 5 January 1994 cited in the application see claims ---	1-27
P,Y	WO,A,95 18124 (MERCK SHARP & DOHME LTD.) 6 July 1995 see claims ---	1-27
P,Y	WO,A,95 16679 (MERCK & CO. INC.) 22 June 1995 see claims ---	1-27
P,Y	WO,A,95 23798 (MERCK & CO. INC.) 8 September 1995 see claims -----	1-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents :

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Date of the actual completion of the international search

28 May 1996

Date of mailing of the international search report

07.06.96

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Authorized officer

Chouly, J

# INTERNATIONAL SEARCH REPORT

1. International application No.

PCT/GB96/00587

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 18-22 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Int. Patent Application No.

PCT/GB 96/00587

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